Am J Hum Genet 38:170–187, 1986

Genetic Interrelationship between Insulin-Dependent Diabetes Mellitus, the Autoimmune Thyroid Diseases, and Rheumatoid Arthritis

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SUMMARY

To investigate the possible coinheritance of autoimmune diseases that are associated with the same HLA antigen, we studied 70 families in which at least two siblings had either type I diabetes mellitus (IDDM), autoimmune thyroid disease (ATD), rheumatoid arthritis (RA), or a combination of these diseases. HLA-A, B, and C typing was performed on all affected sibs in one generation or more. First, we estimated by sib-pair analysis the disease allele frequency (p_D) and the mode of inheritance for each disease. According to the method of ascertainment entered into the analysis, the $\hat{p}_D$ for ATD ranged from .120 to .180, for an additive (dominant) mode of inheritance. For RA, the $\hat{p}_D$ ranged from .254 to .341, also for additive inheritance, although recessive inheritance could not be excluded. For IDDM, the $\hat{p}_D$ ranged from .336 to .337 for recessive inheritance; additive inheritance was rejected. Second, we examined the distribution of shared parental haplotypes in pairs of siblings that were discordant for their autoimmune diseases. The results suggested that the same haplotype may predispose to both IDDM and ATD, or IDDM and RA, but not to both RA and ATD. Analysis of pedigrees supported this hypothesis. In 16 families typed for HLA-DR also, the haplotype predisposing to both IDDM and ATD was assigned from pedigree information to DR3 (44%), DR4 (39%), or DR5, DR6, or DR7 (5.5% each). In some families, these haplotypes segregated over several generations with

Received December 13, 1984; revised June 21, 1985.

This study was supported in part by the Grossman Fund (C. P. T) and grant CA-27632 from the National Institutes of Health (M.-C. K. and B. H.).

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ATD only (either clinical or subclinical), suggesting that in such families, ATD was a marker for a susceptibility to IDDM. In several families, an IDDM haplotype segregated with RA but not with ATD. This suggests that ATD- and RA-associated susceptibilities to IDDM may be biologically different and thus independently increase the risk of IDDM.

INTRODUCTION

Several autoimmune diseases are associated with the same human leukocyte antigen (HLA) specificity [1]; for example, insulin-dependent diabetes mellitus (IDDM), the autoimmune thyroid diseases (ATDs: Graves' disease [GD] and Hashimoto's thyroiditis [HT]), myasthenia gravis, systemic lupus erythematosus (SLE), celiac disease, and Addison's disease are associated with HLA-DR3. DR4-associated diseases include IDDM, rheumatoid arthritis (RA), myasthenia gravis, and primary biliary cirrhosis. Several diseases show an association with more than one DR specificity; for example, IDDM and myasthenia gravis are associated with DR3 and DR4, SLE with DR2 and DR3, and HT with DR3 and DR5. These genetic relations are reflected in clinical and epidemiologic observations that patients with one autoimmune disease, and their relatives, are more likely than might be expected from population prevalence data to express another autoimmune disease associated with the same HLA-DR specificity [2–7].

We refer to diseases that share a particular HLA-DR population association as belonging to the same immunologic cluster. Thus, IDDM and the ATDs are considered to be in the same cluster, as both are associated with HLA-DR3; RA and IDDM are similarly clustered, as both are associated with HLA-DR4. This is not to say, that when IDDM and ATD occur in the same individual or family, they are necessarily associated with a haplotype bearing the HLA-DR3 specificity, or that when RA and IDDM are so found, the implicated haplotype will carry the DR4 specificity. Conversely, RA and the ATDs do not belong to the same immunologic cluster. We proposed that the same allele can predispose to several diseases from the same cluster, but cannot predispose to diseases from different clusters. Aware that we presently cannot determine single allele effects, but rather must consider haplotype effects, we expected these assumptions would be reflected in the segregation of haplotypes in families with several autoimmune diseases.

There are few reports regarding the distribution and segregation of haplotypes in families expressing several autoimmune diseases [8, 9]. For this reason, we analyzed the distribution of shared parental haplotypes in siblings affected with DR3- and DR4-associated diseases—in particular, IDDM, the ATDs, and RA. Pedigrees were recorded to evaluate segregation of the diseases. We assumed that each disease is expressed according to its specific mode of inheritance and penetrance. We first estimated the disease allele fre-

quency (p_D) and mode of inheritance of each studied disease by analyzing the distributions of haplotypes identical by descent (IBD) in sib-pairs who shared the same disease (concordant pairs). We then examined the distribution of haplotypes IBD and the pedigrees of sib-pairs affected by different autoimmune diseases (discordant pairs) to evaluate possible coinheritance of diseases with the same haplotype. In a subsample of families typed for HLA-DR, we assigned haplotypes that appeared to cosegregate with several diseases in the DR3 and DR4 clusters.

MATERIALS AND METHODS

Families in which two or more siblings had ATD, IDDM, RA, or a combination of these diseases were contacted through the Diabetes, Thyroid, and Nuclear Medicine Clinics of the University of California, San Francisco (UCSF), the Rheumatology Clinic at Letterman Hospital (San Francisco, Calif.), the Diabetes Clinic at Pittsburgh University (Pittsburgh, Pa.), and the Kaiser Permanente Medical Group (Oakland, Calif.). Additional sources of families were the Lupus Societies of Marin and Walnut Creek, California, and volunteers from those areas. We ascertained families from four ethnic groups: Caucasian other than Mexican-American, Mexican-American, Asian, and black. Because of the small sample in the Asian and black groups, results for those families are not detailed in this report. We present our results for the Mexican-American and Caucasian families separately because, even though these groups are alike in the pattern of inheritance of diseases within families, their $\hat{p}_D$ values might differ somewhat. Results other than p_D estimates can be generalized to both groups. Anderson et al. [10] similarly pooled Mexican-American and Caucasian families in their study.

Diagnoses were established by the patient's physician or from the patient's medical and treatment histories. We tested all individuals who had not previously been screened for thyroid antibodies at UCSF, except patients with GD, as GD is easily diagnosed and thyroid antibodies are always present. We considered individuals with either microsomal- or thyroglobulin-positive tests to have ATD and those with both tests negative to be free of ATD, except for two patients who had undergone a thyroidectomy for HT more than 25 years before; in such cases, the antibody levels may decrease to normal [11]. Pedigrees were obtained through interviews with all subjects and, whenever possible, with other members of the proband's family.

Blood (30 ml) was drawn in one sampling from each subject: 10–20 ml in ACTD was used for HLA typing, 10 ml in EDTA for red-cell and plasma markers, and 10 ml in a clot tube for serum markers. HLA typing was done using a standard lymphocytotoxicity method [12]; 13 HLA-A, 28 HLA-B, and three HLA-C specificities were tested. We also retyped 16 of the 70 families for HLA-A, HLA-B, and HLA-C, and typed them for HLA-DR with antisera provided by the International Histocompatibility Workshop (Munich, West Germany). Properdin factor B (Bf) variants (S, S1, F, F1) were determined by electrophoresis of plasma on agarose gel followed by immunofixation [13]. Glyoxylase I (GLO) variants 1 and 2 were determined by starch-gel electrophoresis of red cells according to a modification of Kompf et al.'s method [14]. Serum samples were tested for antithyroglobulin antibodies by radioimmunoassay and for antimicrosomal antibodies by the hemagglutination test from Ames Laboratories (Miles, Elkhart, Ind.).

The Sib-Pair Method

The Motro-Thomson extension [15] of the general sib-pair method [16, 17] was used to analyze the concordant sib-pair data for Caucasians; the Mexican-American sample was too small for analysis. This method estimates the p_D from the distribution in sib-pairs of haplotypes IBD according to strict recessive and additive modes of inheritance. For the additive mode, the penetrance of the disease in the heterozygotes vs. homozygotes, λ, is

set at ½; the results are close to those expected for a strict dominant mode, but easier to derive. To correct for selection biases, weighting factors are introduced into the statistical analysis according to three methods of sib-pair ascertainment: (1) incomplete truncate (all families with at least two affected sibs have the same probability of being selected), in which case all affected sib-pairs contribute with equal weight to the analysis; (2) incomplete single selection (families are selected with probabilities directly proportional to their number of affected sibs), in which case each pair is weighted by a factor proportional to the number of affected sibs in the family; (3) incomplete sib-pair selection (families are selected proportional to the number of their affected sib-pairs), in which case each pair is given a weight proportional to the number of affected sib-pairs in the family. The weighting is comparable to the standard procedure in which one sib-pair per family is chosen at random, but entails no loss of information [15].

Results for GD and HT were grouped under ATD assuming that, in families in which both diseases occur, GD and HT share an HLA-associated genetic susceptibility. The similarity of the haplotype distributions in the GD—GD, HT—HT, and GD—HT sib-pairs favors this assumption.

Pooled Data

For diseases with a high allele frequency, a relatively large sample is needed to discriminate with statistical significance between inheritance models. Because of the small sample in our RA and IDDM groups, we extracted all available published data and analyzed the pooled data in order to increase the power of our analysis. The sources of these data and the possible disadvantages of pooling are given in later sections.

Pedigree Studies

Pedigrees were obtained to examine the segregation of haplotypes with one or more autoimmune diseases and to assign specific HLA-DR alleles to high-susceptibility haplotypes within families (fig. 1). Pedigrees were used to estimate the cumulative risk of ATD to mothers of ATD probands by a modified life-table analysis [18].

RESULTS

We ascertained 70 families with at least two sibs with one or more of the following autoimmune diseases: IDDM (DR3 and DR4 clusters), ATDs (DR3 cluster), and RA (DR4 cluster); 12 of these families had affected sib-pairs in more than one generation.

Concordant Sib-Pairs

Table 1 shows the distribution of parental haplotypes IBD in sib-pairs concordant for either ATD, IDDM, RA, or IDDM + ATD, for the total number of families and pairs in each ethnic group; for families with more than one generation of affected sibs, all affected sib-pairs in all generations are included.

Autoimmune thyroid disease: Graves' disease and Hashimoto's thyroiditis. We ascertained 42 Caucasian and four Mexican-American families with one or more sib-pairs with ATD. All ATD distributions showed a greater proportion of pairs sharing two haplotypes IBD and a smaller proportion sharing none, when compared to the 25%, 50%, 25% distribution expected from random segregation. Also, both distributions showed a greater than expected proportion of pairs sharing one haplotype. Because of the small sample in the Mexican-American group, further statistical analysis is done for the 65 Caucasian pairs

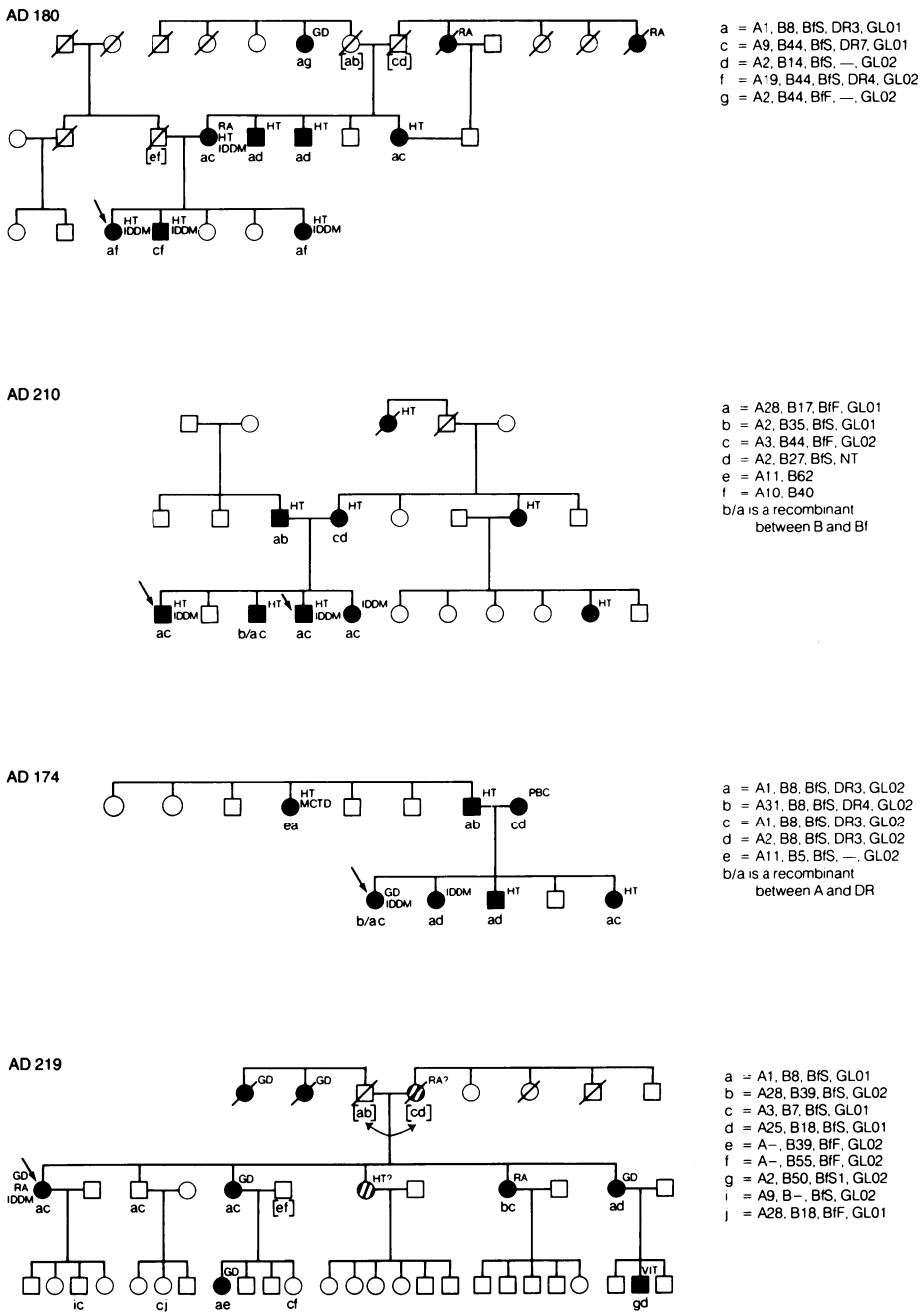

FIG. 1.—Representative pedigrees of families with several HLA-DR3 and HLA-DR4 associated autoimmune diseases. Abbreviations: HT, Hashimoto's thyroiditis; GD, Graves' disease; RA, rheumatoid arthritis; IDDM, insulin-dependent diabetes mellitus; PBC, primary biliary cirrhosis; MCTD, mixed connective tissue disease; VIT, vitiligo. Symbols: ● affected female; ■ affected male; ⊘ probable affected; [ ] genotype derived from pedigree information; ⌣ HLA genotypes are interchangeable.

TABLE 1

DISTRIBUTION (%) OF HAPLOTYPES IBD IN CONCORDANT SIB-PAIRS WITH VARIOUS COMBINATIONS OF AUTOIMMUNE DISEASES, BY ETHNIC GROUP

DISEASE GROUP (SIB 1–SIB 2)	ETHNIC GROUP	NO. FAMILIES	NO. PAIRS	NO. (%) HAPLOTYPES IBD		
				2	1	0
ATD—ATD	Caucasian	42	75	27 (36)	42 (56)	6 (8)
	Mexican-American	4	10	3 (30)	7 (70)	0 (0)
RA—RA	Caucasian	6	6	5 (83)	1 (17)	0 (0)
	Mexican-American	2	3	0 (0)	2 (66)	1 (33)
IDDM—IDDM	Caucasian	11	17	9 (53)	7 (41)	1 (6)
IDDM + ATD— IDDM + ATD	Caucasian	4	6	3 (50)	2 (33)	1 (17)

only (table 2). Because of independence requirements, only sib-pairs from the index generation are entered in the analysis. To apply the Motro-Thomson extension of the sib-pair method [15], the distribution of haplotypes IBD was determined according to the number of affected sibs in each sibship (table 3).

Results of the sib-pair analysis for ATD are shown in table 4 (Study Data). For each mode of inheritance, $\hat{p}_D$s are given for those methods of ascertainment for which the statistical results did not reject the model ($P > .10$, two-tailed test). The recessive model was rejected for incomplete truncate selection ($P < .03$) and for incomplete single selection ($P < .08$). The $\hat{p}_D$s ranged from .120 to .180 for an additive mode of inheritance; for the recessive mode, under incomplete single selection, the $\hat{p}_D$ was .580.

From the analysis of pedigrees of ATD probands, the cumulative risk of ATD to first-degree female relatives was estimated at 50%, also suggesting a dominant mode of inheritance.

TABLE 2

DISTRIBUTION (%) OF HAPLOTYPES IBD FOR CAUCASIAN SIB-PAIRS ENTERED IN THE ANALYSIS (ONE GENERATION PER FAMILY)

DISEASE	SOURCE OF DATA	NO. FAMILIES	NO. PAIRS	NO. (%) HAPLOTYPES IBD		
				2	1	0
ATD	Study	42	65	25 (39)	36 (55)	4 (6)
RA	Study	6	6	5 (83)	1 (17)	0 (0)
	Pooled*	67	86	28 (33)	44 (51)	14 (16)
IDDM	Study	11	17	9 (53)	7 (41)	1 (6)
	Pooled*	348	440	246 (56)	166 (38)	28 (6)

* Source of pooled data. For RA: Stastny [19]; Khan et al. [20]; Strom and Moller [21]; Michalski et al. [22]; Pasquali et al. [23]; Rossen et al. [24]; Zilko and Dawkins [25]; Christiansen et al. [26]. For IDDM: Cudworth et al. [27, 28] per Ewens and Clarke [29]; Barbosa et al. [30, 31]; Bengsch et al. [32]; Ludwig et al. [33] per Thomson [34]; Spielman et al. [35]; Ryder et al. [36]; Deschamps et al. [37] per Clerget-Darpoux and Bonaiti-Pellie [38]; Suciu-Foca et al. [39]; Rubinstein et al. [40]; de Jongh et al. [41]; Murphy et al. [42]; Winearls et al. [43].

TABLE 3

SEGREGATION OF HAPLOTYPES IBD AMONG ATD SIBS ACCORDING TO NO. AFFECTED SIBS IN SIBSHIP

Disease	No. affected sibs/family	No. families	Shared haplotypes	No. pairs
ATD	2	11	*ac/ac*	11
		17	*ac/bc*	17
		4	*ac/bd*	4
	3	8	*ac/ac/bc*	24
		1	*ac/ac/ac*	3
	4	1	*ac/ac/ac/bc*	6
Total		42		65
IDDM	2	4	*ac/ac*	4
		3	*ac/ad*	3
		1	*ac/bd*	1
	3	2	*ac/ac/ad*	6
		1	*ac/ac/ac*	3
Total		11		17

Rheumatoid arthritis. The distribution of haplotypes IBD in the Caucasian and Mexican-American families is shown in table 1 and that in the proband generation of Caucasian families in table 2. All sibships had only one affected sib-pair. We pooled our data with the published data [9, 19–26]; Statsny's results include one randomly chosen sib-pair per sibship [19]. The pooled distribution (table 2) showed a greater than expected proportion of sib-pairs sharing two haplotypes IBD, but showed the expected proportion of sib-pairs sharing one haplotype. This pattern suggests a dominant inheritance [16]. Results of the

TABLE 4

RESULTS OF THE SIB-PAIR ANALYSIS FOR ATD (STUDY DATA), RA (POOLED DATA), AND IDDM (POOLED DATA)

Disease	Mode of inheritance	Ascertainment method*		
		I.T.	I.S.	I.SP.
		A. Study Data		
ATD	Additive	.120 ± .063	.144 ± .078	.180 ± .108
	Recessive	$P < .03$	$P < .08$	.580 ± .113
		B. Pooled Data*		
RA	Additive	.341 ± .149	.296 ± .133	.254 ± .123
	Recessive	.720 ± .108	.686 ± .106	.651 ± .108
IDDM	Additive	$P < .0001$	$P < .0001$	$P < .0001$
	Recessive	.337 ± .029	.338 ± .028	.336 ± .028

NOTE: For source of pooled data, see table 2.
* I.T. = incomplete truncate; I.S. = incomplete single; I.SP. = incomplete sib-pair.

analysis for the pooled data are summarized in table 4. Relatively high disease allele frequencies (.254 to .341 for additive and .651 to .720 for recessive inheritance) are compatible with the estimated data points for all three methods of ascertainment.

Insulin-dependent diabetes mellitus. The distribution of haplotypes IBD in the 11 Caucasian families (table 1) is similar to that reported by others [10, 27–43]. The distribution according to the number of affected sibs in the sibship is detailed in table 3. We added our families to 337 families from published reports that gave the information on sibships required for this analysis (table 4). Additive inheritance was rejected for all methods of ascertainment; recessive inheritance ($\hat{p}_D$ ranging from .336 to .337) was compatible with the data.

Insulin-dependent diabetes mellitus with autoimmune thyroid disease. Four families had two or more sibs with both IDDM and ATD. The sib-pair distribution is shown in table 1.

Discordant Sib-Pairs

Insulin-dependent diabetes mellitus and autoimmune thyroid disease. In families with both IDDM and ATD, we observed every combination of these diseases among the affected sibs (table 5). In most families, the sib affected with IDDM also had ATD (IDDM + ATD). The distribution in which one sib had IDDM + ATD and the other had ATD (IDDM + ATD—ATD) showed a greater proportion of sib-pairs sharing one haplotype IBD than the 50% expected under random segregation or under an additive model for concordant pairs. In contrast, the IDDM + ATD—IDDM pairs shared two haplotypes IBD more often than expected and one and two haplotypes less often than expected. The small number of IDDM—ATD pairs had a higher than expected proportion of pairs sharing 2 and 0 haplotypes IBD. Our results and those from pooled data [44, 45] showed the same trend (table 5).

TABLE 5

DISTRIBUTION (%) OF HAPLOTYPES IBD IN DIFFERENT COMBINATIONS OF IDDM AND ATD SIB-PAIRS, PER ETHNIC GROUP, FOR STUDY DATA AND POOLED DATA

DISEASE GROUP (SIB 1–SIB 2)	SOURCE	ETHNIC GROUP*	NO. FAMILIES	NO. PAIRS	HAPLOTYPES IBD 2	1	0
IDDM + ATD—ATD	Study	C	11	18	3 (17)	14 (78)	1 (5)
		M-A	2	4	2 (50)	2 (50)	0 (0)
	Pool	C	15	27	7 (26)	18 (67)	2 (7)
IDDM—ATD	Study	C	7	7	3 (43)	2 (28)	2 (29)
		M-A	1	2	0 (0)	1 (50)	1 (50)
	Pool	C	10	10	4 (40)	4 (40)	2 (20)
IDDM + ATD—IDDM ...	Study	C	4	4	3 (75)	1 (25)	0 (0)
	Pool	C	6	6	5 (83)	1 (17)	0 (0)

NOTE: For source of pooled data, see text.
* C = Caucasian; M-A = Mexican-American.

Rheumatoid arthritis and autoimmune thyroid disease. The distribution of haplotypes IBD for all possible combinations of RA and ATD in 13 Caucasian and eight Mexican-American families (table 6) showed the same trends. No sib-pairs in the RA + ATD—RA distributions shared two haplotypes IBD. In the RA + ATD—ATD pairs, no pairs shared zero haplotypes; more than 50% shared one haplotype, although only marginally in the Mexican-American distribution. In the RA—ATD distributions, no clear pattern emerged, either because of the small sample or because RA and ATD do not segregate on the same haplotype.

We pooled our 13 Caucasian families with eight Caucasian families from Grennan et al.'s study [9]; all sib-pairs from the index generations were included (table 6). The study and the pooled results showed the same trends.

Insulin-dependent diabetes and rheumatoid arthritis. There were only three sib-pairs with the IDDM—RA combination, two in the Mexican-American and one in the Caucasian group. Two pairs shared one haplotype and the third pair shared two. These results corroborate those in other reports [26]: in nine families, 33% of sib-pairs shared two haplotypes, 66% shared one, and 0% shared none.

DISCUSSION

The results of our concordant sib-pair analysis suggest: (1) for ATD, an additive mode of inheritance; (2) for RA, either an additive or a recessive mode of inheritance; and (3) for IDDM, a recessive mode of inheritance. We interpret the results with caution as the sib-pair method we used tests for strict recessive and additive inheritance for a one-locus, two-allele model. Several factors suggest that this model may not be the best: the low population prevalence of IDDM compared to the relatively high $\hat{p}_D$ values, the reported associations of several autoimmune diseases with other loci (e.g., the polymorphic region

TABLE 6

DISTRIBUTION (%) OF HAPLOTYPES IBD IN DIFFERENT COMBINATIONS OF RA AND ATD SIB-PAIRS, PER ETHNIC GROUP, FOR STUDY AND POOLED DATA

DISEASE GROUP (SIB 1–SIB 2)	SOURCE	ETHNIC GROUP*	No. FAMILIES	No. PAIRS	HAPLOTYPES IBD 2	1	0
RA + ATD—ATD ..	Study	C	7	10	3 (30)	7 (70)	0 (0)
		M-A	4	7	3 (43)	4 (57)	0 (0)
	Pool	C	10	14	4 (29)	10 (71)	0 (0)
RA—ATD	Study	C	5	5	1 (20)	3 (60)	1 (20)
		M-A	2	4	0 (0)	2 (50)	2 (50)
	Pool	C	8	11	3 (27)	5 (46)	3 (27)
RA + ATD—RA....	Study	C	1	1	0 (0)	1 (100)	0 (0)
		M-A	2	2	0 (0)	1 (50)	1 (50)
	Pool	C	3	4	0 (0)	3 (75)	1 (25)

NOTE: Data pooled from Grennan et al. [9].
* C = Caucasian; M-A = Mexican-American.

flanking the insulin locus for IDDM [46] and the Gm locus for ATD [47]), and the possible heterogeneity of the diseases. More complex models, such as a two-locus model with epistatic interaction or a three-allele model with two alleles in negative complementation, should be investigated. Thus, we expect there may be some bias in the estimates of the $\hat{p}_D$s and modes of inheritance. To evaluate the possible coinheritance of haplotypes predisposing to several autoimmune diseases, however, it is sufficient to note that IDDM has a mode of inheritance "close to recessive" in the HLA region and that ATD and RA have a mode of inheritance "close to dominant." Before applying our results to the examination of haplotype segregation in discordant sib-pairs, we evaluate them against known population prevalence data and modes of inheritance.

Possible Biases

The method of ascertainment of sib-pairs can bias the estimation of the p_D and of the mode of inheritance. Our ATD families were ascertained through two or more affected probands (31%), but also through probands with other autoimmune diseases, such as IDDM (36%) and RA (33%). If the mode of inheritance of IDDM is "close to recessive" and both haplotypes can also predispose to ATD, then probands in families with IDDM and ATD are more likely to have two affected parents and selection of these families would increase the $\hat{p}_D$ for ATD: of 15 such Caucasian sibships in our study, 40% had parents who both had ATD. Conversely, if RA and ATD do not share a susceptibility allele, then selection of ATD sib-pairs through families with both diseases would decrease the $\hat{p}_D$. In an unbiased selection, such families would be included in proportion to their occurrence in the population. To evaluate these opposing biases, we compared the haplotype distribution of ATD sibs between families with ATD only and families with ATD and other autoimmune diseases; we found no significant differences.

Similarly, the selection of families with an unusually high number of affected sibs would result in an increased $\hat{p}_D$. The sensitivity of the affected sib-pair method to the effect of data from large families with a large proportion of pairs sharing zero haplotypes is discussed by Ewens and Clarke [29], who consider that a substantial bias in the $\hat{p}_D$ estimates can result from inclusion of a disproportionate number of such families in the analysis. We examined the possibility of pooling our data with the published ATD data [48–53]. Comparison between the number of sib-pairs per family in those 14 families vs. our 42 study families shows substantial differences: 29% vs. 76% of families had one sib-pair per family, 29% vs. 21% had three pairs, 21% vs. 2% had six pairs, and 21% vs. 0% had 10–15 pairs. Many families in prior reports were chosen for study because they were unusual "high-risk families" [48–52]. As such families are rarely seen in the clinical setting and probably are not representative of all ATD families, we chose not to pool the data for ATD.

Another possible bias in studies of chronic diseases with variable age-dependent penetrance is that of misclassification owing to subclinical or unexpressed disease. This does not bias our concordant sib-pair analysis, as only clinically affected sibs were evaluated. Among the discordant sib-pairs, how-

ever, sibs expressing one disease may still be at risk for the discordant disease of their sib. To minimize this bias for ATD, we evaluated all sibs with thyroid antibody tests. As there are no similarly reliable tests for RA and IDDM, some ATD sibs in our IDDM—ATD and RA—ATD pairs could have subclinical or unexpressed IDDM or RA. Also, a few probands susceptible to ATD may not have been detected by our tests because of factors known to lower the expression of this phenotype: a young age, sex (male), pregnancy [54] or because of possible environmental or polygenic factors that may influence the penetrance of the disease. Such misclassification probably weakens the differences between the various haplotypes distributions in discordant pairs.

Concordant Sib-Pairs

1. Autoimmune thyroid disease

Evaluation of the estimated p_D. Our results suggest that about 30% of the Caucasian population is at risk for ATD, whether clinical, subclinical, or unexpressed. Several population prevalence surveys indicate that, by 75 years of age, about 20% of females have abnormal levels of thyroid antibodies [55, 56]. Necropsy data document microscopic evidence of HT in 22% of adult females and 6% of adult males [57]. Low estimates of p_D can be derived from these data, under our assumption that probands expressing subclinical disease are carriers of the same disease allele as those expressing the clinical phenotype. This assumption is supported by the observation that, of asymptomatic patients with positive thyroid-antibody tests, 7.3% per year become symptomatic [58]. Thus, for a dominant mode of inheritance and a prevalence of 20%–30% of ATD, the $\hat{p}_D$ falls between .10 and .15, according to the Hardy-Weinberg law. Although prevalence rates underestimate substantially the lifetime risk for diseases with age-dependent expression, these surveys also point to a high population susceptibility to ATD.

Evaluation of the mode of inheritance. There is no consensus about the mode of inheritance of ATD. Recessive, dominant, and polygenic inheritance have been suggested for both HT [47, 59] and GD [59]. Our results are compatible with a dominant mode of inheritance, but failed to reject a recessive mode of inheritance for the incomplete sib-pair ascertainment. This analysis cannot, however, exclude a two-locus model with epistatic interaction or other genetic models.

Other aspects of our data for the Caucasian and Mexican-American families support a dominant mode of inheritance for ATDs: (1) the cumulative risk of ATD to mothers of ATD patients who did not have sibs with IDDM or RA was estimated at 50%, in agreement with the results of others [2, 60]; (2) in most ATD pedigrees, the disease could be traced to only one parental side of the family, often over several generations; (3) in most families, the same haplotype was found in all members of the family with ATD (see fig. 1, #180 and #219). These patterns are all compatible with a dominant mode of inheritance, but do not exclude more complex models.

2. Rheumatoid arthritis

Evaluation of the estimated p_D. The results of our sib-pair analysis suggest a prevalence of susceptibility to RA on the order of 50%. The actual prevalence

of the clinical disease depends on its penetrance, which has been estimated from twin data to be around 30% [61], although this estimate may be high because of the ascertainment biases of twin data.

Our p_D estimates were compared to both population prevalence and incidence data [62], from which we estimated the cumulative lifetime risk [63] of clinical RA from birth to age 70+ to be close to 8% for females and 4% for males. If penetrance of RA is in the range of 20% to 30% [61], then cumulative risk of susceptibility to RA is 24%–40% (multiplying the estimated lifetime risk for females by a factor of 3–5). From the Hardy-Weinberg law, this is equivalent to a $\hat{p}_D$ of about .13–.22 for a strict dominant or of .49–.63 for a strict recessive mode of inheritance. These estimates are lower than our sib-pair estimates, which may be somewhat high because of possible ascertainment biases or biases in the model. Nevertheless, we agree with others [64] that there is probably a high proportion of susceptibles in the population and a low penetrance of the disease.

Evaluation of the mode of inheritance. The mode of inheritance of RA is not known. Familial aggregation of the disease is weak: first-degree relatives have an age-adjusted relative risk of about 1.7, implying a very low penetrance of a common genetic predisposition, a large proportion of sporadic cases in the population, or both [64]. The higher rate of concordance for monozygous (30%) than for dizygous twins (5%) also implies a genetic etiology [61], as does the population association of RA with HLA markers.

Results of our sib-pair analysis are compatible with a dominant or a recessive mode of inheritance for RA. The number of pooled pairs is too small to reject either model with this analysis. Other methods could help distinguish between the two modes of inheritance: for example, when RA data from the 9th International Histocompatibility Workshop (Munich, West Germany, 1984) were analyzed by the antigen genotype frequency method [65] using HLA-DR4 as the marker antigen, the results were compatible with a dominant model and rejected a recessive model (G. Thomson, unpublished data, 1984).

3. *Insulin-dependent diabetes mellitus*

There is controversy about the mode of inheritance of IDDM [66]; several models (e.g., [29, 34, 35, 38]) have been proposed to explain the discrepancy between the population prevalence of IDDM (about 0.5%) and the high $\hat{p}_D$s and recombination fractions estimated from the first one-locus models. Our $\hat{p}_D$s also are high (close to .34), possibly because the sib-pair method is sensitive to the values of λ and of the recombination fraction R [29]. In the Motro-Thomson methodology [15], λ is set equal to zero for the recessive mode of inheritance and equal to ½ for the additive mode, with R set at zero for both modes. Ewens and Clarke [29], using a maximum likelihood method, showed that substantial changes can arise in the estimation of p_D after changes in λ and R. This may partly explain the high values of our estimates—or possibly the one-locus model is incorrect. Our reason for reexamining the distribution of haplotypes IBD in sib-pairs, however, was to improve our interpretation of the discordant sib-pair results; we noted that affected sibs shared two haplotypes significantly

more often than one haplotype and that the results of our sib-pair analysis are compatible with a "close to recessive" model of inheritance at the HLA locus.

Discordant Sib-Pairs and Their Pedigrees

To clarify the clustering of autoimmune diseases in individuals, families, and populations, we proposed that the same allele or haplotype could predispose to ATD and IDDM, as both diseases are in the HLA-DR3 cluster, or to IDDM and RA, both in the HLA-DR4 cluster; conversely, that the same haplotype could not predispose to ATD and RA, as RA and ATD are not in the same immunological cluster. The haplotype distributions in discordant sib-pairs and their pedigrees were examined for evidence for or against this hypothesis.

1. Insulin-dependent diabetes and autoimmune thyroid disease

In the 18 study families with IDDM and ATD, only seven IDDM probands were known to have ATD at the time of ascertainment. After all probands were tested for thyroid antibodies, however, six additional probands were found to have abnormally high titers of antibodies and were then classified as IDDM + $A^{T}D$. In four of the seven families with an IDDM proband without ATD, the proband carried a haplotype associated with ATD in other members of the family and had factors known to delay expression of ATD (e.g., see fig. 1, #174 and #210); in the other three families, the IDDM proband had neither ATD nor shared a haplotype with an ATD sib.

It is informative to compare the distributions of discordant sib-pairs with the corresponding concordant distributions. If ATD and IDDM share the same predisposing allele and the same mode of inheritance, then the IDDM + ATD—ATD distribution should not differ significantly from the ATD—ATD, the IDDM—IDDM, or the IDDM + ATD—IDDM + ATD distribution. Our results show that these distributions differ substantially. In the IDDM + ATD—ATD distribution, the proportion of Caucasian sib-pairs (67%–78%) who share one haplotype is much greater than the maximum 50% expected under random segregation or under a dominant inheritance for a single disease and is even greater than the 55% observed in the ATD—ATD distribution. Furthermore, only 26% of pairs in this IDDM + ATD—ATD distribution share two haplotypes, as compared to 36% in the ATD—ATD distribution. This suggests that adding the constraint that one sib has IDDM to the condition that both sibs share ATD decreases the probability that the pairs will share two haplotypes IBD without increasing the probability that they share none. This pattern would be expected if ATD has a dominant mode of inheritance and IDDM a recessive one and if both diseases share a predisposing haplotype. Comparing the IDDM + ATD—ATD and the IDDM + ATD—IDDM + ATD distributions shows that the percentage of sibs sharing two haplotypes is increased from 27% to 67%, which is even higher than the 55% found in IDDM—IDDM pairs. Adding the constraint that both diseases be expressed in both sibs increases the probability that both sibs share two haplotypes. Assuming a recessive mode of inheritance for one or both diseases, this pattern is expected if the same haplotype predisposes to both diseases.

2. Rheumatoid arthritis and thyroid disease

If RA and ATD do not share a predisposing allele or haplotype, and if both diseases are inherited dominantly, then the RA—ATD distribution should not deviate significantly from that expected under random segregation and the RA + ATD—RA distribution should show fewer pairs sharing two haplotypes. Our results are in accord with these expectations (table 6). For the RA + ATD—ATD pairs, we expect some misclassification of disease as there was no test to evaluate ATD sibs for subclinical RA and the disease has a low penetrance. Thus, a proportion of ATD sibs could be susceptible to RA and share two haplotypes IBD with their RA + ATD sib. This is apparent in the results of the RA + ATD—ATD pairs. This distribution also shows a greater than expected proportion of sibs sharing one haplotype IBD, as compared to the ATD—ATD distributions; the interpretation is similar to that for the IDDM + ATD—ATD distribution; that is, that ATD is dominantly inherited.

If either RA or ATD were inherited recessively, the distributions including sibs concordant for the recessive disease would show a greater proportion of pairs sharing two haplotypes IBD and a decreased percentage sharing one, as did the IDDM + ATD—IDDM distribution. That neither the RA + ATD—ATD nor the RA + ATD—RA distribution showed this trend favors, but does not prove, our hypothesis.

Grennan et al. [9] reported that although 46% of the 13 RA families in their study had a member with ATD the RA haplotype was not shared with ATD relatives in 75% of these families. They concluded that, if both diseases have a joint susceptibility, it is not HLA-associated. Our results support this conclusion.

3. Insulin-dependent diabetes mellitus and rheumatoid arthritis

The pooled results for the IDDM—RA distribution show that, in all pairs, sibs share one or two haplotypes IBD, with 66% sharing one. This implies, for the same reasons mentioned for the IDDM + ATD—ATD pairs, that the same haplotype can predispose to both IDDM and RA, but that an additional predisposing haplotype is necessary for the expression of IDDM. This second haplotype could carry a susceptibility to both IDDM and ATD. Based on the conclusion suggested by the haplotype distribution of the RA—ATD pairs, the same haplotype could not predispose to all three diseases, suggesting that the ATD-associated and the RA-associated susceptibilities to IDDM are biologically different and independently increase the risk for IDDM. As ATD is in the DR3 or DR5 cluster and RA in the DR4 cluster, these suggestions are in accord with the observed increased risk for the DR3/DR4 heterozygote.

Informative pedigrees of individuals with IDDM + ATD + RA would show independent segregation of the RA and ATD haplotypes. Two such pedigrees are shown in figure 1. In pedigree AD#180, a female has IDDM + ATD + RA: one haplotype (A1-B8-DR3) is found in six other family members with ATD; the other (A9-B44-DR7) comes from her father who had two sisters with RA. In pedigree AD#219, the proband's A1-B8 haplotype is found in all members of the family who have GD, the A3-B7 haplotype in a sib with RA; the proband

has the IDDM + ATD + RA combination. GD comes from the paternal side of the family and RA reportedly from the maternal side. Because of the low penetrance of both IDDM and RA and the different ages at which each disease is expressed, this disease combination is seldom encountered. Additional families are needed to confirm our observations.

Distribution of HLA-DR Antigens Predisposing to IDDM and ATD

From the analysis of pedigrees, it was often possible to assign, with high probability, a haplotype to one or more autoimmune diseases. For example, in three generations of family #180, all members who carried the HLA A1-B8-DR3 haplotype had ATD and three also had IDDM. Assuming a "close to dominant" inheritance for ATD and a "close to recessive" inheritance for IDDM, we presumed that this haplotype predisposes to both diseases. We evaluated in the same way all families in which sufficient relatives had an HLA-DR typing. We expected that, as IDDM and ATD are associated with HLA-DR3, most haplotypes predisposing to both diseases would carry the DR3 antigen. The distribution of the DR specificities in haplotypes presumed to predispose to IDDM and ATD was: DR3 (44%), DR4 (39%), DR5, DR6, and DR7 (5.5% each). Only 44% of all assignable IDDM + ATD haplotypes carried the DR3 antigen. The larger proportion (50%) of non-DR3, non-DR5 haplotypes is consistent with the small relative risk (RR) reported for GD or HT and DR3 (RR = 3–5), or goitrous HT and DR5 (RR = 5). These modest associations indicate that a susceptibility to ATD is often found on haplotypes bearing other specificities. Our results suggest that it is not specifically the serologically defined DR3 or DR4 that predisposes to these autoimmune diseases, but perhaps a DR-associated epitope or a closely associated gene or set of genes in linkage disequilibrium with these antigens. This interpretation does not exclude an epistatic model or, for IDDM, a negative complementation effect within the I-a region of the HLA.

Our data suggest that, in certain families, an HLA-associated susceptibility to IDDM and to ATD may be coinherited and may be expressed solely as ATD, with a dominant inheritance. In such families, ATD would be a marker for a susceptibility to IDDM; two susceptibility haplotypes, however, would be needed for the expression of IDDM. Our results also suggested that a susceptibility to RA and IDDM could be coinherited, but on a haplotype not associated to ATD, as RA and ATD do not seem to share a susceptibility allele in the HLA region. Other diseases in the DR3 and DR4 clusters could also be markers for a susceptibility to IDDM.

ACKNOWLEDGMENTS

We acknowledge particularly the contributions our patients have made toward this research. We thank Drs. Michael Okerlund, John Karam, Peter Singleton, Gary Friedman, Wallace Epstein, Francis Greenspan and Nancy Sanz and Ms. Peggy Huang for giving us access to their patients; Dr. Diane Wagener for providing us with three families and their HLA typing; Ms. Elsie Joe Rie, Ms. Dolores Lattanzio, and Mr. Joe Crandall for their technical expertise; and Ms. Susan Eastwood for editorial collaboration in the preparation of the manuscript.

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